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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,164	03/09/2004	Dale R. Pfost	56548-015	4027

23397 7590 10/30/2006

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EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/797,164	PFOST, DALE R.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-53,55 and 56* is/are pending in the application.

4a) Of the above claim(s) *28-33 and 41-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-40,53,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group III in the reply filed on August 8, 2006 is acknowledged. The traversal is on the ground(s) that while the restriction requirement sets forth the fact that a separate and distinct search would be required for each of the claimed inventions, "the examiner has not explained why such differences would cause a serious burden on part of the examiner." This argument is not found persuasive because the fact that the search for each of the inventions is distinct from one another and are not co-extensive serves as evidence that undue burden would be required to search and examine each of the claimed inventions together. Further, evidence of undue burden to search and examine each of the inventions together is found in the fact that the inventions have acquired a different status in the art as demonstrated by their different classifications and recognized divergent subject matter. Applicants further state that they do not understand what is meant by the fact that the claims are improperly joined and assert that the claims do not in fact a Markush group. This argument is also not persuasive because the claims encompass the detection of a SNP in a target molecule. The two types of target molecules in "patients" which contain SNPs are nucleic acids and proteins. Thereby, although the claims recite the generic word of a target molecule, reading the claims in light of the specification, it is clear that the claims intend to encompass the detection of SNPs in nucleic acids and the detection of SNPs in proteins. As clearly set forth in the Office action of July 10, 2006, nucleic acids and proteins are structurally and functionally distinct molecules and thereby methods which

detect SNPs in nucleic acids and methods which detect SNPs in proteins are considered to be patentably distinct from one another.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 34-40, 53, 55 and 56 have been examined herein only to the extent that the claims read on the elected invention of methods in which a SNP present in a nucleic acid is detected and analyzed to determine its association with response to a therapeutic compound. The subject matter of methods in which a SNP present in a protein is detected and analyzed to determine its association with response to a therapeutic compound (i.e., invention IV) is withdrawn from consideration as being drawn to a non-elected invention. In response to this Office action, claims 34-40, 53, 55 and 56 should be amended so that they are limited to the elected subject matter of group III.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-40, 53, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

The claims are broadly drawn to methods for formulating pharmaceutical compositions for treating a pathology and methods of treatment using said pharmaceutical compositions, wherein said methods comprise measuring a correlation between a genetic variation or polymorphism in a target molecule in a population of patients and the patient's response to a compound, and selecting at least two compounds that provide the greatest percentage of efficacy in the patient population or selecting one therapeutic compound having an efficacy associated with the presence of the polymorphism.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise

definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention."

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, no members of the broadly claimed genus of genetic variations or SNPs associated with a patient's response to treatment with a compound have been described in terms of a particular nucleotide sequence or location within the genome. Further, no compounds have been defined by their chemical structure or specific function. The specification (see Examples 1 and 2) discusses the use of drugs A, B, C, D and E and the response of patients having a different genotype to these drugs. However, the specification does not disclose the identity of these drugs, which SNPs the drugs are associated with, what pathology the drugs treat, or the genotype of the patients. Accordingly, the specification does not provide an adequate written description of a single composition within the scope of the claimed invention.

It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. restriction map, specific biological activity of an encoded protein product, etc.). In the instant case, no such identifying characteristics have been provided for any of the compounds or for any of the genetic variants or SNPs associated with response to treatment with a compound.

Accordingly, the written description requirements have not been met for the claimed genus because a representative number of compounds within the claimed genus have not been defined in terms of their structure or other specific identifying characteristics. While the breadth of the claims is not reasonably quantifiable, it is clear that the genus of compounds that may be included by the claims is enormous. The claims allow for compounds "effective for treating a pathology." Thereby, the claims include compounds that treat any of the diverse pathologies, such as diabetes, Alzheimer's Disease, Cancer, Parkinson's Disease, lupus, AIDS, MS, allergies, malnutrition, depression, drug addiction, gingivitis, epilepsy, etc. etc.... The composition may be used to treat a pathology in a human or any other type of animal. The claims include any type of compound that can be "used to effect a physiological change in treating a pathology" (page 5). Thus, the claims include any type of inorganic or organic compound, such as antisense molecules, antibodies, DNA molecules used for gene therapy, vaccines, enzymes, and receptors. The compounds are defined in terms of modulating the activity of one or more target molecules. The target molecules, may again, be of any structure. As discussed in the specification (page 6), the target molecule "can vary from as large as an association molecules, such as a ribosome or a lipid bilayer, to as small as a small molecule or an ion, such as a hormone, cytokine, cAMP, NO, Ca^{2+}, K^{+}, phosphate, and the like." The compound may modulate the activity of the target compound by any manner. For instance, the specification (page 6) teaches that the compounds may increase or decrease enzyme activity, may increase or decrease gene expression, may increase or decrease protein-protein interaction, may

increase or decrease signal transduction, or may increase or decrease transport or translocation across the membrane. The target compound is described as being associated with one or more SNPs. The specific relationship between the target compound and SNP or other type of genetic variation is not defined. The claims thereby include target compounds that are in any way related, directly or indirectly, specifically or nonspecifically, with a SNP or other type of genetic variation. The SNP or genetic variation may also be from any gene and may occur at any location within the gene.

The specification does not disclose a common structural feature linking the claimed genus of compounds or claimed genus of SNPs and genetic variations. The claims define the compounds in terms of their functional activity, but do not define any of the structural properties of the compounds. While a limited number of specific individual compounds are known in the art which directly modulate the activity of nucleic acids or proteins containing SNPs, the general knowledge in the art concerning therapeutic compounds does not provide any indication of how the structure of one therapeutic compound is representative of other therapeutic compounds. The structure and function of a given compound that modulates the activity of one SNP does not provide guidance as to the structure and function of other compounds that modulate the activity of the same or other SNPs. Therefore, the description in the prior art of specific therapeutic compounds is not representative of the very large genus of compositions containing two or more compounds that are effective for treating a pathology.

Additionally, the claims include compositions that are effective for treating at least 1%, and thereby at least 25%, 50%, 75% or 90% or more of patients having the

pathology. Yet, the specification does not disclose a common structural feature or specific property that is present in compounds and which ensures the compounds are effective for treating at least 1%, 255, 50%, 75% or 90% of patients having the pathology. The claims further include compounds that exhibit no toxicity (i.e., claim 37). However, the specification does not exemplify any compounds that exhibit no toxicity and whose activity is correlated with the occurrence of a genetic variation in a patient population.

For these reasons, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, & 1 Written Description Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-40, 53, 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are broadly drawn to methods for formulating pharmaceutical compositions for treating a pathology and methods of treatment using said pharmaceutical compositions, wherein said methods comprise measuring a correlation between a genetic variation or polymorphism in a target molecule in a population of patients and the patient's response to a compound, and selecting at least two compounds that provide the greatest percentage of efficacy in the patient population or selecting one therapeutic compound having an efficacy associated with the presence of the polymorphism.

The breadth of the claims is significantly large. The claims first require the analysis of a SNP or genetic variation in the genome of any population of patients (i.e., humans, dogs, cats, birds, pandas etc). The claims require determining an association between a SNP or genetic variation and the response of a population of patients to treatment with a compound. The claims do not set forth the identity of the SNP/genetic variation – i.e., its nucleotide identity or location within a particular gene or sequence within a genome. The claims also do not set forth any particular pathology that is to be

treated using the composition of compounds. Thereby, the claims include the use of compositions of compounds that are to be used to treat any of the diverse pathologies, such as diabetes, Alzheimer's Disease, Cancer, Parkinson's Disease, lupus, AIDS, MS, allergies, malnutrition, depression, drug addiction, gingivitis, epilepsy, etc. The composition may be used to treat a pathology in a human or any other type of animal.

The claims include any type of compound that can be "used to effect a physiological change in treating a pathology" (page 5). Accordingly, the claims include any type of inorganic or organic compound, such as antisense molecules, antibodies, DNA molecules used for gene therapy, vaccines, enzymes, and receptors. The compounds are defined in terms of modulating the activity of one or more target molecules. The target molecules, may again, be of any structure. As discussed in the specification (page 6), the target molecule "can vary from as large as an association molecules, such as a ribosome or a lipid bilayer, to as small as a small molecule or an ion, such as a hormone, cytokine, cAMP, NO, Ca^{2+}, K^{+}, phosphate, and the like." The compound may modulate the activity of the target compound by any manner. For instance, the specification (page 6) teaches that the compounds may increase or decrease enzyme activity, may increase or decrease gene expression, may increase or decrease protein-protein interaction, may increase or decrease signal transduction, or may increase or decrease transport or translocation across the membrane. The target compound is described as being associated with one or more SNPs or genetic variations. However, the relationship between the target compound and SNP is not

defined. The claims thereby include target compounds that are in any way related, directly or indirectly, specifically or nonspecifically, with a SNP or genetic variation.

Additionally, the claims include compositions that are effective for treating at least 1%, and thereby at least 25%, 50%, 75% or 90% or more of patients having the pathology. Yet, the specification does not disclose a common structural feature or specific property that is present in compounds and which ensures the compounds are effective for treating at least 1%, 255, 50%, 75% or 90% of patients having the pathology.

The claims further include the use of compounds that are exhibit no toxicity. However, the specification does not define any particular structural feature which ensures the compounds will exhibit no toxicity.

Nature of the Invention:

The claims encompass methods of formulating pharmaceutical compositions and treatment methods using said pharmaceutical compositions wherein the compositions contain compounds whose efficacy is correlated with the occurrence of a SNP or other genetic variation in a patient's genome. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

As set forth above, the claims encompass methods which require the use of a phenomenally large genus of compounds, wherein the compounds are not defined in

terms of any specific structural or functional property. Yet, the specification does not provide a single example of a specific compound that falls within the scope of the claims. The specification (see Examples 1 and 2) discusses the use of drugs A, B, C, D and E and the response of patients having a different genotype to these drugs. However, the specification does not disclose the identity of these drugs, which SNPs the drugs are associated with, what pathology the drugs treat, or the genotype of the patients. The specification does not exemplify any particular SNPs or other types of genetic variations which are correlated with a patient's response to treatment with a particular compound or set of compounds.

The prior art of Smith-Sorensen (British Journal of Cancer. 1998.78: 375-381; see page 377-378) teaches that ovarian cancer patients with TP53 mutations have a significantly better response to paclitaxel / cisplatin combination therapy as compared to cyclophosphamide / cisplatin therapy. However, the specification as originally filed does not disclose this specific association between the occurrence of a mutation and response to therapy and thereby cannot be relied upon as enabling this particular subject matter.

Amount of Direction or Guidance Provided by the Specification:

The specification provides a general description of a research project which one might undertake in order to try to identify compositions which fall within the scope of the claims. For example, the specification (page 10) states that methods for identifying SNPs are known in the art. It is also stated that methods are known in the art for analyzing a SNP in order to determine if it is associated with a pathology (page 11).

Once a SNP associated with a disease has been identified, one should then screen compounds, in vitro or in vivo, in order to try to identify compounds that may be effective at modulating the activity of a target molecule (pages 14 and 18). The specification teaches that compounds should be selected which, when used in combination, remain effective and do not result in a toxic response.

Clearly, the described research project provides only an invitation to experiment. While methods for analyzing SNPs and therapeutic compounds may be known in the art, providing methods of searching for compounds is not equivalent to providing specific compounds that can be used to treat specific pathologies by modulating the activity of specific target molecules correlated with specific SNPs. Further, while the prior art teaches compounds that modulate the activity of a SNP, such limited teachings directed to specific SNPs associated with specific diseases are not sufficient to support the enablement of the broadly claimed invention of any combination of compounds that modulate in any manner any SNP present in any gene and associated with any pathology. The experimentation required to identify the compounds present in the claimed compositions is extensive and highly unpredictable and would not be considered by the artisan to be routine. The novel aspect of the claims is the combination of compounds that modulate the activity of a SNP or genetic variation associated with a pathology. The novel aspects of the invention are not the process steps of sequencing to identify a SNP or other genetic variations, performing linkage and associated studies to identify SNPs or other genetic variations associated with a pathology, or performing general screening methods to identify a compound that

modulates the activity of a SNP or other genetic variation since these general methodologies are well known in the art.

The Predictability or Unpredictability of the Art:

The art of identifying SNPs and other types of genetic variation associated with a pathology and associated with a population of patient's response to treatment is highly unpredictable. Knowledge of the sequence of a gene does not allow one to immediately envision specific polymorphisms and mutations which are correlated with a pathology and a response to treatment. Even after a new polymorphism or mutation is identified, it remains unpredictable as to whether that polymorphism or mutation is correlated with the occurrence of a disorder and a response to treatment to that disorder. In the human genome alone, a SNP occurs once every 1000 nucleotides. However, the vast majority of these SNPs are not correlated with the occurrence of any particular disorder or response to treatment. Thereby, one cannot predict apriori what will be the structure of a SNP or genetic variation that is correlated with response to a compound.

The unpredictability of establishing a correlation between a polymorphism and response to therapy is exemplified by the teachings of Wadler (The Cancer Journal from Scientific American. 1997. 3: 284-288). Wadler (see abstract and page 287) reports that although ras mutations are strongly associated with the occurrence of colorectal cancer, ras mutations do not have a significant predictive value for response to treatment of colorectal patients with 5-FU and IFN. Thereby, although a mutation may be associated with the occurrence of a disease, it remains highly unpredictable as to whether that mutation will be associated with response to treatment for the disease.

The art of identifying therapeutic compounds that modulate the activity of a molecule associated with a SNP is also highly unpredictable. One cannot also predict a priori what will be the structure or function of a compound that is associated with a SNP or genetic variation and which will be effective to treat at least 1% of a patient population having a pathology.

There is no common structural feature which links therapeutic compounds and which would allow one to ascertain without undue experimentation whether a compound will modulate the activity, expression etc of a target molecule that is directly or indirectly associated with a SNP. Given the lack of a specific structure-function relationship between SNPs and the occurrence of a pathology, the lack of a specific structure-function relationship between therapeutic compounds and the ability to modulate target molecules and the lack of a specific structure-function relationship between therapeutic compounds and the ability to treat a pathology, one can only identify SNPs, target molecules and therapeutic compounds through extensive experimentation. Additionally, the specification does not provide any specific guidance as to how to identify compounds that have these attributes when used in combination. Combinations of compounds can only be identified through random, trial-by-error experimentation. The specification emphasizes the unpredictability of identifying compounds that can be used in combination to effectively treat a pathology. The specification points out that each compound will may have a different effect, such that the effect of one compound may negate the effect a second compound. It is also well known and accepted in the art that compounds may interfere with one another and may in combination cause toxic side-

effects. The specification does not provide any guidance as to how to determine a priori which combinations of two, three or more compounds can be used together to effectively treat a pathology. Such information can be obtained only through experimentation.

The teachings of Lucentini (The Scientist. December 2004, page 20) highlights the unpredictability in the art of establishing an association between a mutation/polymorphism and the occurrence of a disease or condition and a response to therapy. As discussed by Lucentini, reproducible association studies are 'few and far between." The reference reports that 'when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

Working Examples:

The specification provides only a hypothetical example of formulating a pharmaceutical composition for treatment of a pathology. The specification does not provide any specific examples of SNPs or genetic variations associated with a pathology and response to therapy and does not provide any specific examples of formulating a pharmaceutical composition and treating a patient with a pharmaceutical composition containing compounds wherein the compounds are correlated with a SNP that is associated with a patient's response to treatment.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not disclose a single SNP or other type of genetic variation associated with a pathology and associated with a patient's response to treatment with a compound. Additionally, the specification does not exemplify single composition containing one, two, three or more compounds that have therapeutic efficacies correlated with the presence of at least one SNP.

Further, the specification does not provide the novel aspects of the invention – i.e., the SNPs/genetic variations associated with response to treatment and the structure and function of chemical compounds whose efficacy is correlated with a SNP or genetic variation. Rather, the novel aspects of the invention can only be supplied through extensive experimentation. In view of the high level of unpredictability in the art

and the lack of specific guidance and working examples provided in the specification, undue experimentation would be required to practice the broadly claimed invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-40, 53, 55 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34-37 and 40 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final step of the claims. The claims are drawn to methods of formulating a pharmaceutical composition. However, the final step is one of selecting compounds. The claims do not clearly recite a step of using the selected compounds to formulate a pharmaceutical composition. Thereby, it is not clear as to the methods are ones for formulating a pharmaceutical composition or ones for selecting compounds.

Claims 34-37 are indefinite over the recitation of "wherein said percentage is at least 1% of the total patient population having said pathology" because the phrase "said percentage" lacks proper antecedent basis. The claims do not previously refer to a percentage of the patient population, but rather refer to a percentage of efficacy. Thereby it is unclear as to what is intended to be meant by "wherein said percentage is at least 1% of the total patient population having said pathology."

Claims 38-40 are indefinite over the recitation of "SNP associated with said target molecule" (see claim 38) and "SNPs associated therewith" (see claim 40). The

specification states that a "target molecule that is 'associated with' or 'correlated with' a particular genetic variation, preferably a particular SNP, is a molecule that can be functionally distinguished in its structure, activity, concentration, compartmentalization, secretion, and the like, as a result of such genetic variation." However, this teaching does not provide a clear and complete definition for what is intended to be encompassed by target molecules associated with SNPs. It is unclear as to whether the target molecule contains a SNP (e.g., a nucleic acid or protein that contains a SNP) or if the target molecule is in some other way associated with a SNP (e.g., the target molecule itself does not contain a SNP but other members of this class of compounds contains a SNP, or the target molecule is a part of a cycle / cascade involving numerous other compounds in which one of the other compounds contains a SNP or alters the activity or expression of a SNP or creates the formation of a SNP). Accordingly, it is unclear as to what is intended to be the relationship between the target molecule and the SNP.

Claims 38 and 39 are indefinite because the phrase "said combination" lacks proper antecedent basis.

Claim 53 is indefinite and vague over the recitation of "identifying a sub-population of patients." While the claim states that it is a property of the sub-population that it contains a SNP, the claims do not clearly set forth the criteria for identifying the sub-population of patients. That is, it is not clear as to whether the sub-population is identified based on the fact that they contain a SNP or based on some other unstated criteria. Further, the claim is indefinite over the recitation of "all patients exhibiting said

pathology." This phrase is not clearly defined in the specification or the claim and it is unclear as to what constitutes "all patients." For example, it is unclear as to whether the phrase "all patients" is intended to refer to all currently known patients, all currently known and unknown patients, all past and future known or unknown patients or to all patients in a particular study.

Claims 55 and 56 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final step of the claims. The claims are drawn to methods of preparing a combination of compounds. However, the final step is one of calculating the efficacy of a first and second compound. The claims do not clearly recite a step of using the compounds to prepare a combination of compounds. Thereby, it is not clear as to the methods are ones for preparing a combination of compounds or ones for analyzing the efficacy or toxicity of a compound.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith-Sorensen (British Journal of Cancer. 1998.78: 375-381).

Smith-Sorensen (page 377) teaches a method comprising the steps of measuring a correlation between a genetic variation in a target molecule in a population of patients and a response to therapy and selecting two compounds that provide the

greatest percentage of efficacy in said population. In particular, Smith-Sorensen teaches a methods which measures the correlation between the occurrence of p53 mutations and response to combination treatment with paclitaxel / cisplatin and to cyclophosphamide / cisplatin. Smith-Sorensen (page 377-378) found that patients with TP53 mutations had a significantly better response to paclitaxel / cisplatin combination therapy as compared to cyclophosphamide / cisplatin therapy. In the absence of evidence to the contrary, the response to therapy is considered to represent at least 1% of the total patient population.

Regarding the recitation in claim 34 of "formulating a pharmaceutical composition" and in claim 40 of "method of formulating a therapeutic composition," as noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "method of formulating a pharmaceutical composition" and "method of formulating a therapeutic composition" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the

claims. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 39, 53 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith-Sorensen.

Smith-Sorensen (page 377) teaches a method comprising the steps of measuring a correlation between a genetic variation in a target molecule in a population of patients and a response to therapy and selecting two compounds that provide the greatest percentage of efficacy in said population. In particular, Smith-Sorensen teaches a methods which measures the correlation between the occurrence of p53 mutations and response to combination treatment with paclitaxel / cisplatin and to cyclophosphamide / cisplatin. Smith-Sorensen (page 377-378) found that patients with TP53 mutations had a significantly better response to paclitaxel / cisplatin combination therapy as compared to cyclophosphamide / cisplatin therapy. In the absence of evidence to the contrary, the response to therapy is considered to represent at least 1% of the total patient population. Smith-Sorensen teaches a retrospective study in which the occurrence of TP53 mutations in ovarian cancer patients are assayed for following

treatment of a patient in order to determine an association between the occurrence of TP53 mutations and response to treatment.

Regarding claims 38, 39, and 53, Smith-Sorensen does not teach treating the patients with paclitaxel and cisplatin following the detection of TP53 mutations.

However, in view of the teachings of Smith-Sorensen of an association between TP53 mutations and improved response to paclitaxel and cisplatin combination therapy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Smith-Sorensen so as to have first analyzed ovarian cancer patients for the occurrence of TP53 mutations and then to have treated those patients having TP53 mutations with paclitaxel / cisplatin combination therapy, rather than cyclosphosphamide / cisplatin therapy, in order to have provided a more effective means for treating ovarian cancer in patients having TP53 mutations.

Regarding claim 39, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have administered the paclitaxel and cisplatin simultaneously since Smith-Sorensen teaches that these two chemotherapeutic agents are administered to patients simultaneously (see page 376-377).

Regarding claim 55, Smith-Sorensen teaches determining a correlation between TP53 mutations and response to the combination of paclitaxel and cisplatin therapy. Smith-Sorensen does not teach separately analyzing the association between TP53 mutations and response to paclitaxel treatment alone and cisplatin treatment alone. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have separately analyzed the correlation between TP53

mutations and response to treatment with paclitaxel alone and cisplatin alone in order to have provided further information regarding the association between the TP53 mutations and response to treatment which would be helpful in further optimizing the pharmaceutical compositions and treatment regimens.

7. Claims 35 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith-Sorensen in view of Pamukcu (U.S. Patent No. 6,235,776).

The teachings of Smith-Sorensen are presented above.

Regarding claims 35 and 56, Smith-Sorensen does not teach using a composition of three compounds to treat ovarian cancer patients.

However, Pamukcu (see, e.g., paragraphs 35 and 130) teaches methods for treating ovarian cancer using the chemotherapeutic agents paclitaxel and cisplatin. Pamukcu teaches further treating ovarian cancer patients with cGMP-specific phosphodiester (PDE) inhibitors in order to increase the efficacy of treatment with the chemotherapeutic agents. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have included additional compounds in the pharmaceutical composition, and particularly to have added a cGMP-specific PDE inhibitor to the pharmaceutical composition, in order to have increased the efficacy of the pharmaceutical composition.

8. Claims 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith-Sorensen in view of Masson (Clinical Pharmacokinetics. April 1997. 32(4): 324-343).

The teachings of Smith-Sorensen are presented above.

Regarding claims 36 and 37, Smith-Sorensen does not specifically teach that the pharmaceutical compositions exhibit minimal toxicity or no toxicity.

However, Masson teaches that chemotherapeutic agents exhibit variable toxicity in patients and that toxicity is significantly effected by dose and treatment regimens. Masson teaches that individualized chemotherapy dosing regimens can be developed for each patient in order to minimize toxicity to chemotherapeutic agents.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Smith-Sorensen so as to have formulated pharmaceutical compositions having minimal toxicity or pharmaceutical compositions that exhibited no toxicity with respect to particular organs, in order to have increased the safety and thereby overall efficacy of the pharmaceutical compositions for particular patients. It is further noted that the claims do not specify a particular type of toxicity and thereby include compositions that exhibit minimal or no toxicity with respect to particular cells or organs.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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